Metastatic melanoma (MM) is the most aggressive type of skin cancer contributing to approximately 80% of all skin cancer related deaths. In 2016, it was estimated that more than 76,000 cases would be diagnosed in the United States. The high metastatic potential and aggressive clinical behavior of this disease makes it a major health problem. As a consequence there has been notable development in novel targeted (i.e. BRAF inhibitors) and immune therapies (i.e. anti-PD1 and CTLA4 inhibitors) leading to enhanced overall survival. However, despite improvements in patient outcomes, most patients develop resistance within 6-11 months of dual BRAF/MEK inhibition, and 5 months on immune therapy, highlighting the need to identify new therapies that improve disease management and patient survival. Increased expression of CyclinD1 has been reported to occur as a mechanism of resistance to BRAF inhibition which also plays a role in reactivation of the canonical activating pathway in melanoma, MAPK. Thus, we hypothesized that targeting cyclin D1 using a CDK4/6 inhibitor (Cdk4/6i) may enhance antitumor activity of standard of care when combined with a BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi). We tested our hypothesis using patient derived xenograft (PDTX) and patient derived cell lines. The novel triple therapy drug combination (BRAFi/MEKi/CDK4i) was tested under two scenarios in PDTX models: 1) a naïve setting with established tumors and 2) a salvage setting where tumor growth had escaped standard of care (BRAFi/MEKi) treatment. We tested our hypothesis using patient derived xenograft (PDTX) and patient derived cell lines. The novel triple therapy drug combination (BRAFi/MEKi/CDK4i) was tested under two scenarios in PDTX models: 1) a naïve setting with established tumors and 2) a salvage setting where tumor growth had escaped standard of care (BRAFi/MEKi) treatment.

**Working hypothesis**

Targeted therapies and immune therapies are two of the most effective therapies for patients with MM. However, most often patients develop resistance to either treatment modality. There are many mechanisms of drug-related resistance within tumor cells, including evasion of the immune system, activating mutations, activation of compensatory signaling pathways, and protein upregulation. Increased expression of cyclin D1 has been reported to occur in a portion of cases that are resistant to BRAF inhibition. Thus, we hypothesized that targeting cyclin D1 may enhance antitumor activity of current standard of care in patients with MM.

**Therapeutic treatment responses in PDTX mouse models match those observed in patients**

Novel combination therapy causes partial and near complete response in metastatic melanoma patient-derived preclinical models. The data are compelling and 2) a salvage setting where tumor growth had escaped standard of care (BRAFi) and immune therapies (i.e. anti-PD1 and CTLA4) in the United States. The high metastatic potential and aggressive clinical behavior of this disease makes it a major health problem. As a consequence there has been notable development in novel targeted (i.e. BRAF inhibitors) and immune therapies (i.e. anti-PD1 and CTLA4 inhibitors) leading to enhanced overall survival. However, despite improvements in patient outcomes, most patients develop resistance within 6-11 months of dual BRAF/MEK inhibition, and 5 months on immune therapy, highlighting the need to identify new therapies that improve disease management and patient survival. Increased expression of CyclinD1 has been reported to occur as a mechanism of resistance to BRAF inhibition which also plays a role in reactivation of the canonical activating pathway in melanoma, MAPK. Thus, we hypothesized that targeting cyclin D1 using a CDK4/6 inhibitor (Cdk4/6i) may enhance antitumor activity of standard of care when combined with a BRAF inhibitor (BRAFi) and MEK inhibitor (MEKi). We tested our hypothesis using patient derived xenograft (PDTX) and patient derived cell lines. The novel triple therapy drug combination (BRAFi/MEKi/CDK4i) was tested under two scenarios in PDTX models: 1) a naïve setting with established tumors and 2) a salvage setting where tumor growth had escaped standard of care (BRAFi/MEKi) treatment. We tested our hypothesis using patient derived xenograft (PDTX) and patient derived cell lines. The novel triple therapy drug combination (BRAFi/MEKi/CDK4i) was tested under two scenarios in PDTX models: 1) a naïve setting with established tumors and 2) a salvage setting where tumor growth had escaped standard of care (BRAFi/MEKi) treatment.

**Results**

**Conclusion**

Novel combination therapy causes partial and near complete response in metastatic melanoma patient-derived preclinical models.